

1 of life-threatening complications of post-op
2 hemorrhage."

3 We need to comment on whether there was
4 adequate information to support the statement.

5 DOCTOR CRITTENDEN: I don't think it's
6 there. I think there's anecdotal evidence but for
7 that statement, I'm not sure I saw data that would
8 support that. That's a bit strong. I think it's
9 efficacious but that particular thing, I'd have a hard
10 time approving that.

11 DOCTOR WITTES: I agree. I don't see the
12 data.

13 DOCTOR LASKEY: We've heard anecdotes
14 which are very persuasive but it's certainly not in
15 the panel pack. So I think that that language
16 certainly is an overstatement.

17 Questions relating to safety and
18 effectiveness, #3. Based on the information provided
19 in the PMA, please discuss whether the information
20 supports reasonable assurance of safety and
21 effectiveness of the BioGlue.

22 Well, let's take that one before we go to

1 safety and labeling. Are we all comfortable with the
2 effectiveness of BioGlue as outlined in the
3 application?

4 DOCTOR AZIZ: I think the information
5 presented in the clinical experience I think does
6 validate that.

7 DOCTOR LASKEY: And the safety of the
8 product as well.

9 DOCTOR CRITTENDEN: I guess it depends on
10 what you mean. It's like Bill Clinton said. It
11 depends on what reasonable is. I think in the short
12 term we know, but in the long term, we all have
13 experience with glutaraldehyde preserved pericardium,
14 etcetera, valves and, over time, what they do and we
15 don't know what this is going to do over the long
16 term, over years and years and years and years. But
17 I suppose it's reasonable from what we have in the
18 application anyway.

19 DOCTOR LASKEY: I' think reasonable
20 assurance is the appropriate language here.

21 Questions related to safety and labeling.

22 One aspect of the PMA of a new product is the review

1 of its labeling. The labeling must indicate which
2 patients are appropriate for treatment. Identify
3 potential adverse events with the use of the device
4 and explain how the product should be used to maximize
5 benefits and minimize adverse effects.

6 We're asked to address the following
7 questions regarding product labeling. A) Please
8 discuss the findings of the immunogenicity testing,
9 especially as they relate to both physician and
10 patient labeling issues.

11 Should patients be advised of specific
12 adverse events to be aware of that may suggest they
13 are experiencing a sensitization reaction from the
14 BioGlue?

15 DOCTOR AZIZ: I think they should.

16 DOCTOR LASKEY: There are warnings and
17 precautions in the IFU for patients with a known
18 history of sensitivity to bovine products and BSA.
19 How much further are we recommending the language go?

20 DOCTOR, FERGUSON: My question is what
-21 would that language include because I don't know
22 enough about sensitization, I guess, but what would be

1 useful to put in the labeling that would indicate what
2 they should watch for down the line?

3 MR. DILLARD: I might just maybe clarify
4 the question a little bit. I think, as Doctor Laskey
5 mentioned, currently in the labeling we're talking
6 about known histories to bovine product, BSA,
7 etcetera, and I think that what we're concerned about
8 maybe goes a little bit along the lines of what Doctor
9 Crittenden said. Just we're at that point in time
10 where we have both safety and effectiveness
11 information more in the short term and could this be
12 a product since it is around for quite some number of
13 years 'potentially?

14 I mean we certainly saw with some of the
15 animal results that BioGlue was present, even out to
16 a year. If there is a long-term or delayed
17 sensitization reaction potential associated with the
18 device, not that we've had a lot of experience with
19 putting that into labeling, but I think the question
20 was back to you as clinicians. Is there something
21 that you think would be important to at least discuss
22 and/or suggest to patients and the clinicians about

1 what the long-term potential may be in an area where
2 we don't have the long-term data to support that? I
3 don't know that we were going any farther than that,
4 I mean in terms of what our question was. And the
5 company may have some comment on that, too.

6 DOCTOR LASKEY: My own feeling -- and I'm
7 not an immunologist -- is that it has to be a very low
8 frequency event, that from everything we've heard in
9 the absence of IGE stimulation, this is unlikely to be
10 an anaphylactic response but if it is, it's likely to
11 be extremely infrequent and there's a possibility that
12 there may be delayed hypersensitivity to exposure to
13 bovine products subsequently and we have no way to
14 quantitate that other than to again advise and caution
15 the user in this sense in just that kind of language
16 without putting numbers on it. What is the in-house
17 feeling with respect to the immunogenicity?

18 DOCTOR COSELLI: From a clinical
19 standpoint, we use to a great extent bovine
20 pericardial patches intracardiac and for peripheral
21 vascular patches routinely. We use bovine pericardial
22 aortic valves as a permanent prosthesis. We implant

1 bovine collagen as a hemostatic agent and a protanen
2 is -administered, so just from a clinical standpoint,
3 there's a great deal of use of bovine material in our
4 current practices, many of which are also associated
5 with exposure to glutaraldehyde.

6 DOCTOR FRONK: To address it from the
7 company perspective, I would echo not only Doctor
8 Coselli's comments but also yours, Doctor Laskey. I
9 think we believe that the frequency is very, very low.
10 We haven't seen in any of the patients in the U.S.
11 that have received the product and, as Doctor Vander
12 Wyk mentioned, we estimate over 5,000 patients in the
13 U.S. have been treated with BioGlue over the last
14 almost two years.

15 From a long-term perspective, Doctor
16 Crittenden, the aortic dissection trial, we have
17 patients out past two years on receiving that. Maybe
18 Doctor Coselli and Bavaria, who have the longer term
19 experience with it, can comment on that. But to our
20 knowledge, we have not seen anything ill towards the
21 BioGlue or the patients with longer term exposure.

22 DOCTOR BAVARIA: And I'm presently

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1 following I think at least 40 patients treated for
2 acute type aortic dissection long-term in my clinic,
3 and we've had no long-term issues out to three years
4 now with BioGlue for aortic dissections.

5 DOCTOR LASKEY: Well, I mean we're
6 stumped. We're not experts and we don't have the
7 data, but what data is available would suggest that
a it's an extremely low frequency event. I think
9 heightened awareness is advised.

1 0 Doctor Bavaria, one question. If you
11 can't give someone porcine-derived heparin, what is
12 the alternative? I mean there's pork mucosal,
13 heparin. Is there another commercial source for
14 heparin? I'm ashamed to admit this since I use
15 heparin every day.

16 DOCTOR COSELLI: I'm ashamed to admit the
17 same thing. I don't know.

18 DOCTOR LASKEY: Does anybody in this room
19 know of in patients with a pork or pork-related
20 product allergy and you can't give them heparin.

21 DOCTOR AZIZ: Heparin can be bovine or
22 pork.

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1 DOCTOR LASKEY: That's what I'm thinking
2 so perhaps you might advise not to administer heparin
3 derived from a bovine source in those patients. Is
4 that fair?

5 DOCTOR AZIZ: I think if they don't have
6 an allergic reaction, I think, as Doctor Coselli
7 mentioned, a lot of the patients do get bovine
a products.

9 DOCTOR LASKEY: It's just that the heparin
10 is given systemically and the other stuff is not put
11. into the blood stream.

12 DOCTOR AZIZ: I think it'll be difficult
13 to control that. Let's say they go for cardio-
14 catherization. They get a bit of heparin. How are
15 you going to control?

16 DOCTOR COSELLI: I've never really given
17 it a thought that if somebody has a porcine aortic
18 valve in and I'm doing a re-operation for aorta or
19 coronaries or something not to go ahead and give
20 heparin systemically in the,usual way and never really
21 had any clinical problems with it.

22 DOCTOR LASKEY: Then we'll let the issue

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1 rest. Are you happy?

2 MR. DILLARD: Yes. Thank you.

3 DOCTOR LASKEY: b) the sponsor conducted
4 several animal studies to assess the potential for
5 BioGlue to elicit an immune reaction. The information
6 from these studies suggests that there may be a
7 potential for sensitization to BSA and related
a proteins in the formulation. Information from the
9 clinical studies is limited to assessing the product
10 with short-term follow-up, as we just discussed.
11 Sensitization reactions may occur longer-term, as we
12 discussed, theoretically they may. We have no handle
13 on incidents.

14 Please discuss whether sensitization has
15 been adequately addressed with the clinical data as
16 supplied. I think we just did that. Is that correct?
17 Are additional post-approval studies needed to assess
18 the immune potential of BioGlue? My own read is that
19 this is such a low frequency event that it's probably
20 not feasible to either organize or conduct such a
21 study.

22 MR. DILLARD: Thank you.

1 DOCTOR LASKEY: #5) Please comment on the
2 indications for use section as to whether it
3 identifies the appropriate patient population for
4 treatment with this device. The indications from the
5 current labeling read BioGlue Surgical Adhesive is
6 indicated for use as an adjunct to standard methods of
7 cardiac and vascular repair such as sutures or staples
a to provide hemostasis. I thought that was very clear.
9 I didn't think there was any ambiguity.

10 #6) Please comment on the directions for
11 use as to whether they adequately describe how the
12 device should be used to maximize benefits and
13 minimize adverse events. Again, with the exception of
14 Doctor Ferguson's question about how to get a dry
15 field, and I'm not a surgeon, they seem -perfectly
16 clear to me. The videos were even clearer. Is there
17 anything that we feel needs to be added to the
18 directions for use?

19 DOCTOR CRITTENDEN: It just seemed to me--
20 I've not used it so I don't have any experience with
21 it -- but that it's important to do it with a aorta
22 that's still cross-clamped or perhaps even a heart

1 that's still cross-clamped. That's an issue. I'm
2 looking through this trying to look for that in there
3 and I don't remember reading it before. So if it's
4 not there, some statement about that I think is
5 appropriate.

6 DOCTOR AZIZ: I think the thing is if
7 you're going to use circ arrest, you may not have to
a cross-clamp the aorta. so I think I wouldn't
9 specifically insert that statement. I think the dry
10 field should take care of that.

11 DOCTOR COSELLI: Just to speak to that,
12 that is concomitant with an identical to a dry field.

13 DOCTOR CRITTENDEN: Circ arrest?

14 DOCTOR COSELLI: Circ arrest or cross-
15 clamping. To achieve a dry field, you have to either
16 have systemic circulatory arrest for an arch
17 replacement or localized circulatory arrest if you're
18 dealing with a peripheral vascular procedure.

19 DOCTOR BAVARIA: I've been using the word
20 unpressurized.

21 DOCTOR CRITTENDEN: I like that better.
22 how's that? Unpressurized.

1 DOCTOR LASKEY: So noted.

2 #7) Do we have any other recommendations
3 regarding the labeling of this device?

4 DOCTOR WITTES: I would like changes in
5 table 5 and table 6 consistent with what I said
6 before.

7 MR. DILLARD: Did you say tables 5 and 6?

a DOCTOR WITTES: Tables 5 and 6, 5 because
9 of the correlation and 6 because I don't think that
10 the means and the minimum and maximum tell the story
11 of the number of transfusions. They've very simple
12 changes.

13 DOCTOR LASKEY: Thank you. Well then, I
14 would move to the open public hearing. Is there
15 anyone in the audience who wishes to address the panel
16 before the vote? In that case, I will close the
17 public hearing. Thank you.

18 Do we have an executive secretary to read
19 the voting options or shall I do that?

20 MR. DILLARD: No. I have them. These are
21 the panel recommendation options for pre-market
22 approval applications. The medical device amendments

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1 to the federal Food, Drug and Cosmetic Act as amended
2 by the Safe Medical Devices Act of 1990 allows the FDA
3 to obtain a recommendation from an expert advisory
4 panel and designated medical device pre-market
5 approval applications that are filed with the agency.

6 The PMA must stand on its own merits and
7 your recommendation must be supported by safety and
8 effectiveness data in the application or by applicable
9 publicly available information.

10 Safety is defined in the Act as reasonable
11 assurance based on valid scientific evidence that the
12 probable benefits to health under conditions on
13 intended use outweigh any probable risks.

14 Effectiveness is defined as reasonable
15 assurance that in a significant portion of the
16 population the use of the device for its intended uses
17 and conditions of use will provide clinically
18 significant results.

19 Your recommendation options for the vote
20 are as follows. Approval. If there are no conditions
21 attached. Approvable with conditions. The panel may
22 recommend that the PMA be found approvable subject to

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1 specified conditions such as physician or patient
2 education, labeling changes, or a further analysis of
3 existing data. Prior to voting, all of the conditions
4 should be discussed by the panel.

5 Not approvable. Third option. The panel
6 may recommend that the PMA is not approvable if, #1
7 the data do not provide a reasonable assurance that
8 the device is safe or if a reasonable assurance has
9 not been given that the device is effective under the
10 conditions of use prescribed, recommended or suggested
11 in the proposed labeling.

12 Following the voting, the chair will ask
13 each panel member to present a brief statement
14 outlining the reasons for their vote.

15 Doctor Laskey.

16 DOCTOR LASKEY: I'd like to ask for a
1 7 motion now from the panel members, please.

18 DOCTOR AZIZ: I would recommend that the
19 product be approved with conditions.

20 DOCTOR CKITTENDEN: Second.

21 DOCTOR LASKEY: Okay. And before we vote,
22 may we hear the condition. Is it one condition or

1 several?

2 DOCTOR AZIZ: I think we should encompass
3 some of the things to be talked about, particularly
4 the bovine allergy and things of that nature. Dry
5 field.

6 DOCTOR LASKEY: So for the record as well
7 as for me, what are we placing as a condition with
8 respect to the bovine allergy issue?

9 DOCTOR AZIZ: I think if a patient has a
10 history of bovine allergy, that should be a
11 contraindication. I think a lot of them have been
12 covered in the data that was submitted to us.

13 DOCTOR CKITTENDEN: A contraindication,
14 you're saying?

15 DOCTOR AZIZ: No, no. There should be
16 suspicion. There should be a caution in patients with
17 a history of bovine allergy.

18 DOCTOR LASKEY: Wasn't that in the IFU?

19 DOCTOR FKONK: Yes, it is. It is clearly
20 a contraindication in our labeling. Patients with
21 known sensitivities to bovine products or albumen.

22 DOCTOR LASKEY: Do you then want to revise

1 the placement of a condition on this motion?

2 DOCTOR CKITTENDEN: Can I ask one of the
3 investigators. If you knew this in a patient who was
4 having a problem with an anastomosis that you thought
5 was best treated with BioGlue versus a pledget or a
6 suture, would you withhold using this device? Would
7 you not use this in someone --

8 DOCTOR BAVARIA: Who had a known allergy?
9 Yes. I would not use this. I would use something
10 else.

11 DOCTOR LASKEY: I am hearing the absence
12 of conditions on Doctor Aziz's motion.

13 DOCTOR CRITTENDEN: I think there were
14 some labeling issues that we talked about, so that's
15 one condition. I guess I'm a little miffed now
16 because if there's a strong contraindication but we're
17 not putting anything about surveillance of this, I
18 thought it was minuscule in importance but it seems
19 maybe it's not.

20 DOCTOR LASKEY: So should we then ask for
21 an element of post-marketing surveillance?

22 DOCTOR CKITTENDEN: I don't see where we

1 couldn't. They're going to be followed any way. Just
2 a- simple yes/no that a clinician can say does a
3 patient exhibit any untoward reaction and that's a
4 yes/no. I think that would be simple if they're going
5 to be followed anyway.

6 DOCTOR WITTES: I don't actually
7 understand how this would work. Is that typical
8 whenever there's a contraindication to ask for data
9 collection?

10 MR. DILLAKD: Generally, and this is a
11 confusing point so I'll spend 30 seconds maybe to talk
12 about it. We at the agency generally look at a
13 contraindication as either a clinical situation where
14 we have data where there are going to be adverse
15 patient consequences associated with the use of the
16 product and that may come from either clinical
17 experience or sort of general usage where a labeling
18 may be changed, and then the other would be if there
19 is logically from a clinical standpoint good reasons
20 without testing it in patients why it would not be a
21 wise clinical situation to utilize the product. Then
22 those generally get included also.

1 I think in this case because of our
2 understanding of sensitivity associated with bovine
3 products and the outcomes and the reactions that we
4 have seen before with other products, that we don't
5 need to test this in a bovine-sensitive patient in
6 order to know that perhaps clinically there could be
7 an adverse outcome associated with it. So that also
8 then would be a reasonable situation to put as a
9 contraindication. It would not be general principle
10 for us under that guise to try to force the company to
11 get data to reconfirm that it's not very good in
12 certain circumstances to use the product.

13 DOCTOR LASKEY: Ergo, are there any
14 other--

15 DOCTOR CRITTENDEN: No. I withdraw my
16 plea for that surveillance and we'll just stick with
17 that one condition about the labeling that we
18 discussed earlier.

19 DOCTOR FEKGUSON: Pardon my confusion.
20 Isn't it in there?

21 MR. DILLAKD: Let me just clarify
22 something again real quick. In terms of conditions

1 for your motion, you can place a condition on the
2 manufacturer otherwise agreeing to the fact that the
3 way their labeling is is, appropriate. It's not
4 absolutely necessary that that be a condition if
5 you're comfortable with the way in which it's already
6 worded. So I think either way could certainly be
7 appropriate under this situation. So I don't think we
8 need to get fixated on that.

9 DOCTOR CRITTENDEN: But specifically what
10 I was talking about was the claim about the life-
11 threatening hemorrhage and that was one thing that we
12 didn't want. Maybe I'm being picayunish about it.

13 DOCTOR LASKEY: No. We agreed on that and
14 I had forgotten about that so that actually is
15 something now that we can attach to the motion. With
16 that exception, anything else? Great. So we have a
17 motion on the table.

18 MR. DILLARD: Can I ask for one
19 clarification before you call for a vote on the motion
20 just because I did hear Doctor Wittes' comment on a
21 reanalysis and I was just curious whether or not you
22 thought it was substantial enough to add as a

1 condition or was that sort of a recommendation to the
2 FDA to take a look at?

3 DOCTOR WITTES: Yes. That's why I was
4 being quiet. I don't see it as a condition. I would
5 be very disappointed if you didn't do it, but I don't
6 see it as a condition.

7 MR. DILLARD: Thank you.

8 DOCTOR LASKEY: Do we have enough members
9 to vote?

10 MR. DILLARD: Yes.

11 DOCTOR LASKEY: In that case, can we vote
12 on the motion that's before us to approve with the
13 single condition that the language referring to life
14 threatening hemorrhage be eliminated. All in favor.

15 (Ayes)

16 DOCTOR LASKEY: Opposed.

17 (None)

18 DOCTOR LASKEY: Mike, just to wrap up,
19 just to iterate why you voted as you did.

20 DOCTOR CRITTENDEN: I voted for BioGlue to
21 be approved because I thought the product was
22 demonstrated to be safe and efficacious and, short of

1 this one condition that we talked about, I thought the
2 presentation was good and it deserves to be used by
3 everyone.

4 DOCTOR FERGUSON: I echo that.

5 DOCTOR AZIZ: I echo that. I think it
6 clearly has been shown to be safe and effective and I
7 think it'll impact in a positive way the way we treat
8 some of these difficult patients.

9 DOCTOR LASKEY: Doctor Wittes.

10 DOCTOR WITTES: I found the data
11 convincing, as well.

12 DOCTOR LASKEY: Mr. Morton? Mr. Dacey?
13 No further comments?

14 I believe we are finished with the
15 business at hand this morning, and I'd like to adjourn
16 this meeting and I'd like to thank everyone for a
17 heroic devotion to the cause of duty in view of this
18 morning's tragic events. Thank you all.

19 MR. DILLARD: One quick announcement.
20 Thank you, Doctor Laskey. If everybody could just
21 stay put for a couple of minutes, I'm going to run out
22 and see if I can't learn anything. I will be right

1 back. Thank you.

2 DOCTOR LASKEY: Thank you, CryoLife.

3 (Off the record briefly at 10:55 a.m.)

4 MR. DILLARD: If I could have everyone's
5 attention. The update to this point is that all
6 federal facilities have been closed and we are
7 currently discussing with some of our senior
8 management what the impact that might have on this
9 advisory panel meeting. So I think we have concluded
10 the morning's activities and I think we may need,
11 until we reconvene, to understand the impact that it
12 might have on the afternoon's activity.

13 What I'd like to suggest is that we
14 currently do as I suggested this morning which is
15 unless we hear otherwise, I'd like to go ahead and
16 proceed and try to handle the second PMA this
17 afternoon. If you can come back in an hour at noon, we
18 will try to reconvene and if I have any new
19 information,. I'll be able to announce it at that
20 point. Thank you very much.

21 (Whereupon, the meeting was adjourned at
22 10:58 a.m.)

CERTIFICATE

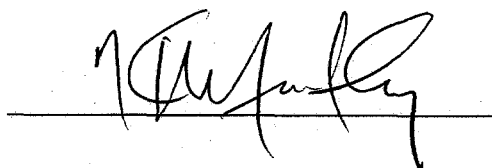
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Before: DHHS/FDA/CDRH

Date: September 11, 2001

Place: Gaithersburg, MD

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A handwritten signature in black ink, appearing to be "J. M. F. Kelly", is written over a horizontal line.